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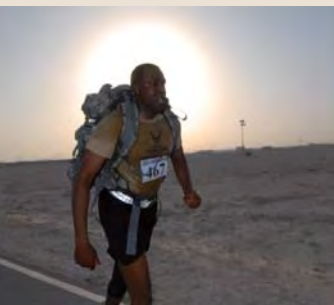
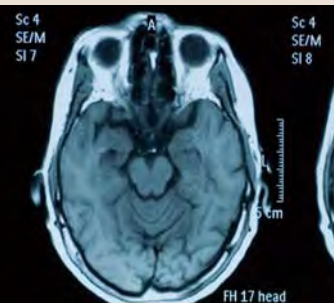
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Initial Assessment of Impact of Adenovirus Type 4 and Type 7 Vaccine on Febrile Respiratory Illness and Virus Transmission in Military Basic Trainees, March 2012

Charles H. Hoke, Jr, MD, Anthony Hawksworth, Clifford E. Snyder, Jr, JD, PhD

After a 12-year hiatus, military recruit training centers resumed administration of adenovirus type 4 and type 7 vaccine, live, oral (adenovirus vaccine) to trainees beginning in October of 2011. Subsequently, rates of febrile respiratory illnesses (FRI) and adenovirus isolations markedly declined. These findings are consistent with those of a placebo-controlled efficacy trial conducted prior to the vaccine's licensure by the U.S. Food and Drug Administration. Continued surveillance will clarify the longer term impact of vaccine use.

Acute respiratory infections caused by strains of adenovirus have long been recognized as common illnesses among military recruits during basic training.¹ First identified in military personnel in 1954, adenoviruses were found to be responsible for 60-80 percent of cases of acute respiratory disease among recruit trainees.² The introduction in 1971 of oral vaccines against adenovirus types 4 and 7 for use among military trainees dramatically reduced the incidence of adenovirus disease and febrile respiratory illnesses (FRI) in that population.^{1,3-5} In 1996 the manufacturer of the vaccine ceased production, and the last doses of the vaccine were administered to trainees in 1999. In subsequent years, the incidence of FRI increased markedly at basic training centers.^{2,6-9} Outbreaks of FRI due to adenoviruses were identified, and deaths associated with adenovirus infections have been reported.^{10,11}

Following the exhaustion of the adenovirus vaccine supply in 1999, military medical leaders explored options by which a replacement vaccine could be acquired. Meetings with regulatory agencies and prospective manufacturers were held, and funding sources sought. Civilian advisory bodies strongly endorsed an effort to restore the vaccine.¹² Funding was provided by the Army Surgeon General in 2000 and subsequently by the Defense Health Program.

The Directorate of Combat Doctrine and Development at the Army Medical Department Center and School drafted, and the Army approved, a requirements document describing the performance characteristics of a replacement vaccine. The Army Medical Research and Materiel Command implemented a formal oversight process to govern all medical product acquisition efforts and chartered an Integrated Product Team of subject matter experts charged with fielding a replacement vaccine to meet the specified requirements.¹³

In 2001, the U.S. Army Medical Research Acquisition Agency awarded Barr Pharmaceuticals a contract to restore the vaccine capability. The company constructed a manufacturing facility, obtained subcontractors, manufactured pilot lots of vaccine, filed an Investigational New Drug application with the U.S. Food and Drug Administration (FDA), and organized clinical trials. Army and Navy investigators conducted studies of the vaccine's safety, immunogenicity and efficacy at Fort Sam Houston, Texas, Fort Jackson, South Carolina, and the the Naval Recruit Training Command Great Lakes, Illinois. Data from these trials demonstrated that the vaccine was safe, efficacious, and immunogenic.^{14,15}

To speed vaccine availability, the Army awarded an initial production contract while the company sought FDA approval for the vaccine. In March 2011,

the FDA approved the company's application to market Adenovirus Type 4 and Type 7 Vaccine, Live, Oral (adenovirus vaccine).¹⁶ The two-tablet adenovirus vaccine was introduced to incoming trainees at recruit training centers (RTCs) in the last week of October and first weeks of November 2011.

Since the mid 1990s, the Naval Health Research Center has conducted population-based respiratory illness surveillance at the RTCs. These ongoing disease surveillance efforts were used to estimate the impact of the newly reintroduced adenovirus vaccine on both FRI rates and the numbers of viruses identified in ill trainees. This preliminary report describes early indicators of FRI incidence at the training installations as well as numbers of clinical isolates of type 4 adenovirus since the reintroduction of the vaccine.

METHODS

After extensive logistical preparation including cold chain testing, the new adenovirus vaccine was deployed in October 2011 to the basic training posts of all of the military services. Personnel from the Military Vaccine Agency traveled to each training facility to assure that appropriate vaccine information was available and that other preparations for vaccine administration had been completed.

The Naval Health Research Center (NHRC) conducted surveillance for rates of FRI and for types of pathogens in upper respiratory swabs obtained from personnel with FRI on 8 of the 9 basic training installations. Dedicated surveillance personnel identified trainees meeting a FRI case definition of fever of 101.5°F or higher and upper respiratory illness symptoms and collected case data and specimens on a convenience sample of up to 20 cases per week. FRI rates were reported as numbers of cases per 100 trainees per week.

Respiratory specimens were received at NHRC every 1-2 weeks and tested for adenovirus and influenza viruses. From 1997-2005, viral cell culture was performed. In 2005 PCR testing became the primary testing mode with cell culture performed on all negative and a subset of adenovirus-positive specimens.

RESULTS

Vaccine shipments began on 18 October 2011, or week 43 of 2011, and have continued without interruption. By mid-November, all incoming (i.e., newly arriving) basic trainees were receiving vaccine. As of 12 March 2012, approximately 63,000 doses had been administered (**Figure 1**).

Detailed temperature monitoring indicated that the temperatures in all vaccine shipping containers have remained within the allowed range of 2 to 8°C. With minor exceptions, vaccine administration has proceeded smoothly. One trainee chewed a tablet, but no ill effects were noted. Three tablets had minor defects related to imperfect coating and were returned to the manufacturer who implemented a 100 percent inspection program.

Febrile respiratory illness rates

Since vaccine introduction in October/November 2011, combined data from all installations under surveillance demonstrate a sustained downward trend in rates

of febrile respiratory illness (FRI rates), with overall rates declining 75 percent from about 0.6 cases/100 trainees/week to about 0.15 cases/100 trainees/week (**Figure 1**).

Laboratory findings

Prior to resumption of the adenovirus vaccine, approximately two-thirds of recruit samples were adenovirus-positive and the majority, typically over 80 percent, were characterized as adenovirus type 4 (The remainder of adenovirus positives were a variable combination of adenovirus types 7, 3, C, 14, and 21, each detected sporadically). After the vaccine was resumed, the proportion of cases from which adenoviruses in general and type 4 in particular were identified markedly decreased. Specifically, monthly proportions positive for adenovirus between October 2011 and January 2012 were 75 percent, 76 percent, 26 percent, and 1 percent, respectively, and the proportions positive for type 4 were 71 percent, 68 percent, 18 percent and 0 percent, respectively (**data not shown**). Vaccine-type adenovirus type 4p was identified in swabs from three trainees since resumption of vaccination.

EDITORIAL COMMENT

It is unusual for a new vaccine to be deployed virtually simultaneously to an entire population at risk (all basic trainees) at a time when the population is under

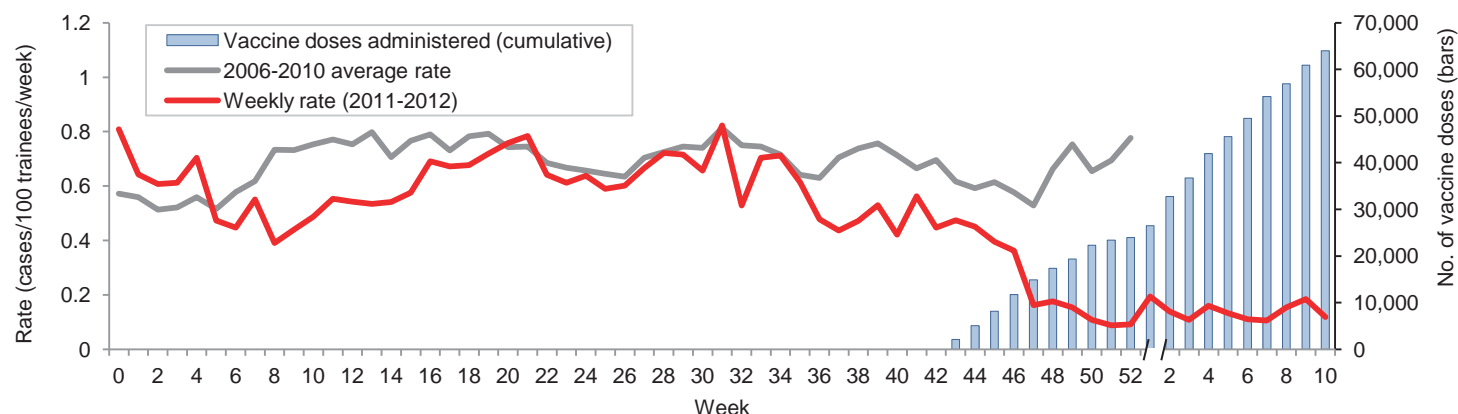
detailed surveillance for the disease against which the vaccine is designed to protect. The respiratory virus and FRI surveillance of basic trainees being conducted at the same time as the adenovirus vaccine deployment allowed an assessment of the vaccines' impact on adenovirus-caused FRI.

Thus far, data suggest that the adenovirus vaccine is highly effective in preventing FRI due to adenovirus type 4. The surveillance findings of an initial 75 percent reduction in FRI and a substantial reduction in numbers of adenovirus type 4 in respiratory swabs are consistent with findings from a controlled, randomized, blinded trial conducted in volunteers at two basic training facilities, in which there was a 99.3 percent reduction in FRI due to adenovirus type 4.¹⁶

Another adenovirus serotype, adenovirus type 14, is not contained in the adenovirus vaccine and has become a concern.¹⁷ During 2007-2009, adenovirus 14 caused multiple short lived, but notable, outbreaks.^{18,19} More recently, type 14 associated cases were detected at the Marine Corps training centers in San Diego, California (from January through August of 2011) and Parris Island, South Carolina (from August 2010 until present). Ongoing surveillance will ascertain whether this serotype, or any other, emerges as a substantial cause of FRI.

The identification of three specimens containing vaccine-type adenovirus type 4p was not unexpected at this point in the

FIGURE 1. Febrile respiratory illness (FRI) rates in 2011-2012, average FRI rates during 2006-2010 (lines), and cumulative adenovirus vaccine doses administered in 2011-2012 (bars), by week, U.S. military basic trainees



immunization program, since one such isolate had been obtained in the phase 3 trials conducted in support of licensure. Surveillance for such isolates, mandated by the Food and Drug Administration as a condition of licensure, will reveal the isolates' extent and importance.

Assuming that the adenovirus vaccine continues to successfully control the impact of adenovirus types 4 and 7 in basic trainees, and that FRI rates remain low, a challenge in the future will be to sustain the commitment to immunization. Experience with the adenovirus vaccine demonstrates that a highly effective vaccine can be lost if it is so good that the need for the vaccine becomes inapparent. The return of epidemic adenovirus disease in 1999, following decades of successful control, should serve as a reminder that epidemic activity may return if the vaccine is withdrawn in the future. Restoring a vaccine capability can be costly and require many years to complete.

The Department of Defense (DoD) has a pressing obligation to protect all service members against illnesses that may be acquired specifically because of their military service.²⁰ Although sporadic outbreaks of adenovirus-associated disease have been noted in other populations, the combination of sustained transmission and relatively high and predictable attack rates of adenovirus-associated disease appears to be unique to U.S. military basic trainees. The earlier loss of the vaccine, whatever the cause, should not be repeated. In 1999, the Armed Forces Epidemiological Board recommended that the DoD consider the concept of a "vaccine and immunobiologics oversight board."²¹ Such a board might facilitate the sustainment of the adenovirus vaccine and other vaccines of military importance.

The initial reduction in FRI and adenovirus type 4 isolates described in this report reflect a preliminary assessment of the vaccine's impact. Longer term observations will be necessary to 1) confirm the initial assessment of the benefits of the vaccine and 2) assess the emergence, or lack of emergence, of non-4,7 adenoviruses among recruits as time passes.

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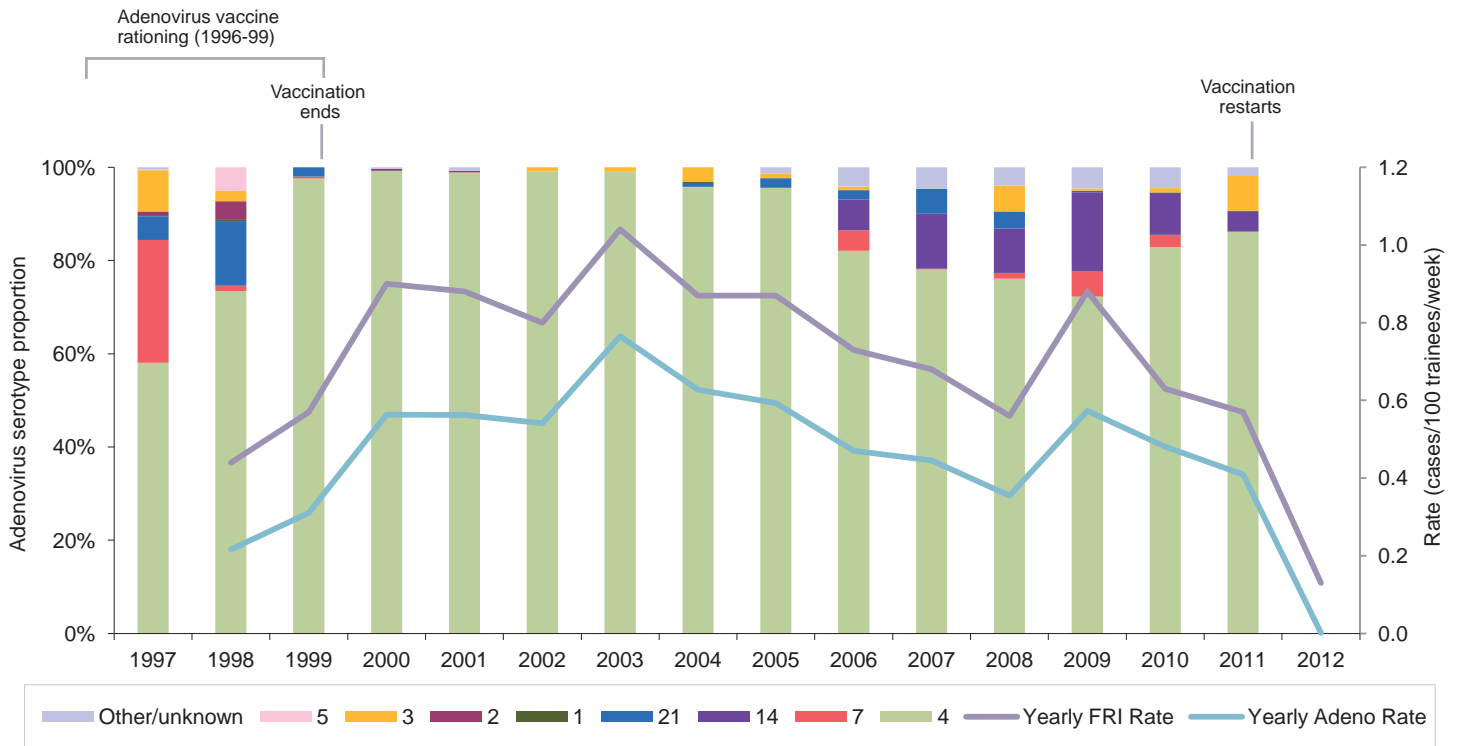
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Surveillance Snapshot: Adenovirus Among U.S. Military Recruits

Febrile respiratory illness (FRI), adenovirus infection^a and adenovirus serotype distribution, by year, U.S. military recruits, 1997-2012



^a Estimates of the proportion of FRI due to adenovirus are based on samples of up to 20 upper respiratory swabs sent weekly from each of 8 recruit training installations. FRI rates not available for 1997. Only one case of adenovirus (Ad14) has been detected to date in 2012.

In 1996, the sole manufacturer of the adenovirus vaccine permanently ceased production. Stocks of vaccine were exhausted in 1999. During the 12 years in which trainees were not vaccinated, the proportion of febrile respiratory illness (FRI) that was due to adenovirus was 68 percent (range: 63-76% per year). Type 4 adenovirus was predominant throughout this period, but re-emergence of group B adenoviruses (e.g., serotype 14) was seen in 2006 and persisted at varying levels through 2011.

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Case Report: Chest Pain in Service Members Following Smallpox Vaccination

Jay R. Montgomery, MD; COL Renata Engler, MD, Frances Allan-Martinez, FNP, Ann Morse, FNP, Laurie Duran, ANP

Vaccines are extremely safe, but rare serious adverse reactions can and do occur in susceptible individuals. A few serious adverse events are predictable and thus avoidable, but the majority occur unexpectedly.

Post-vaccination myopericarditis is one such unexpected adverse event. It is associated most often with the smallpox vaccine, but has also been reported in temporal association with other ACIP-recommended vaccines as well. The immunopathology of vaccine-associated myocarditis/pericarditis (myopericarditis) is distinctly different from that of viral myocarditis.

Vaccinia-associated myopericarditis occurs predominantly in Caucasian male primary vaccinees. While the majority of cases appear to recover clinically within a few weeks, the long-term natural history is unknown. For individuals presenting with unexpected chest pain, shortness of breath, and/or palpitations, a complete evaluation, including a vaccination history, and a heightened index of suspicion will aid in correctly diagnosing, reporting, and managing post-vaccination myopericarditis.

CASE 1

A 21-year-old Caucasian male in good health noted left-sided jaw, neck, shoulder, and chest pain radiating to mid-sternum, and mild shortness of breath while working out (**Figure 1**).¹ The symptoms became worse with deep inspiration and lying down, but improved when sitting up. Naproxen resolved his symptoms. By the next morning, the jaw, neck, shoulder and chest pain (4/10 severity on the visual analogue scale) returned. He presented for medical evaluation and was prescribed ibuprofen for musculoskeletal pain. Later he noted shortness of breath, diaphoresis, and



FIGURE 1. Chest pain and dyspnea after exercise

increased chest pain with climbing ladders. He returned to the medical clinic the next day with increasing chest pain (7/10) and continued dyspnea. He was prescribed tramadol and released with the diagnosis of costochondritis. The patient returned for further evaluation 8 hours later with severe (10/10) chest pain.

On the third visit, the physical examination revealed a soft mid-systolic rub. Electrocardiogram (ECG) showed normal sinus rhythm with ST segment elevation and T wave inversion in leads V5 and V6. Serum troponin I level was significantly elevated with serial testing increases. Clinically relevant elevations in creatine kinase (CK), MB fraction (CK-MB), and the inflammatory marker C-Reactive Protein (CRP) were also noted. Echocardiogram showed a normal ejection fraction (EF=55%), a dilated right ventricle, but no wall motion abnormalities. Chest x-ray (CXR) was normal. Cardiac MRI showed patchy areas of inflammation within the myocardium consistent with myocarditis (**Figure 2**). Patient had received smallpox vaccination 10 days before symptom onset.

CASE 2

A 26-year-old Caucasian male awoke noting constant retrosternal pressure. Within 12 hours, the pain intensified to 7/10. At the local emergency department, after an exam, ECG and CXR, he was diagnosed with musculoskeletal pain. Ketorolac resolved the pain and he was released to duty. When he awoke the next morning, the chest pain was more intense (8/10) and radiating to his left shoulder. He also noted an increase in his heart rate and the sensation of his heart beating harder. He returned to the emergency department and was again treated with ketorolac along with ranitidine and naproxen. An ECG was repeated and the patient was again diagnosed with musculoskeletal pain and released. Nine hours later he returned to the emergency department with severe (10/10) chest pain.

On the third visit, although earlier ECGs showed “nonspecific ST elevation”, the ECG now showed pan-ST elevations with PR interval shortening. Cardiac



FIGURE 2. Gadolinium enhanced cardiac MRI

enzymes (CK, CK-MB, Troponin-I) were significantly elevated. The patient had received smallpox and influenza vaccinations 7 days before symptom onset.

CASE 3

A 22-year-old Caucasian male developed 3/10 upper chest discomfort, chills, and body aches 2 hours after eating. This pain worsened overnight, awakening him twice. The next morning he was noted to be pale and was sent for medical evaluation. His chest pain was worse lying on his back. Sitting up, the pain was associated with a "weight on chest" sensation and increased dyspnea. Exertion worsened his chest pain and shortness of breath. He was evaluated, diagnosed with atypical chest pain, given ibuprofen and acetaminophen/oxycodone, and released. Approximately 18 hours later, he awoke with 7/10 sharp substernal chest pain. He returned for evaluation appearing pale and clammy with increasing chest pain and dyspnea that worsened with leaning forward.

On the second visit, the ECG showed ST elevation in all leads with AVR inversion. CXR was normal. Laboratory studies revealed elevated white blood cell count (WBC) and cardiac enzymes (shipboard screening dipstick troponin/CK-MB). Twelve hours later, the WBC had further increased while the screening cardiac enzymes were negative. Ashore, the more sensitive cardiac enzyme assays showed elevated levels. The patient had received a smallpox vaccination 18 days before symptom onset.

EDITORIAL COMMENT

Each of these young, healthy, Caucasian, male service members with neither cardiac risk factors nor preceding viral illness and who presented with the acute onset of chest pain required multiple medical evaluations before post-vaccination myopericarditis was correctly diagnosed.

While the differential diagnosis of chest pain is broad, healthcare providers must have a heightened index of suspicion for vaccine-associated myopericarditis in healthy young patients even if cardiac disease would generally not be suspected. Whenever such patients present with acute chest pain, dyspnea, and/or palpitations, post-vaccination myopericarditis is possible and can only be ruled out with serial cardiac enzyme measurements. A history of vaccination within 30 days of symptom onset is sufficient to include myopericarditis in the differential diagnosis.

Prior to March 2003, myopericarditis after smallpox vaccination was seldom reported in the United States, although a 1983 study of Finnish recruits estimated the incidence of post-smallpox vaccination myocarditis to be 1:10,000.² In 2004, the DoD reported a statistically significant association between developing myopericarditis and being a white male primary vaccinee.³ The observed incidence of myopericarditis within 30 days after smallpox vaccination is reportedly between 1:6,200 and 1:1,900 but is higher in prospective studies if asymptomatic measures of cardiac injury are included.^{4,5} Re-vaccinees show no increased risk of myopericarditis.³

Vaccine-associated myopericarditis, unlike viral myocarditis, represents an immune hypersensitivity reaction rather than direct infection of the myocardium.^{6,7}

While the vast majority of vaccine-related myopericarditis is associated with vaccinia, myocarditis has also been reported in temporal association with Influenza, Meningococcal, Hepatitis B, DPT, and other vaccines.^{6,7,8} Symptom onset occurs between 7-14 days after immunization in the majority of cases.⁹

Patients usually resolve their clinical symptoms within a few weeks, but some have persistent altered functional capacity and/or clinical symptoms, particularly fatigue. Accurate and timely diagnosis is critical to assure optimum clinical management and follow-up for possible delayed complications such as arrhythmias.

Approximately 175,000 U.S. service members are vaccinated against smallpox annually.¹⁰ It is incumbent upon providers caring for military service members to be skilled in the recognition and treatment of vaccine-associated myopericarditis. A diagnosis and treatment algorithm can be found on the Vaccine Healthcare Centers Network website: www.vhcinfo.org and consultative services are available 24/7 to assist in the management of vaccinees developing adverse events following any vaccination (866-210-6469).

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Predictive Value of Surveillance Case Definitions of Guillain-Barré Syndrome in Vaccine Safety Assessment

Guillain-Barré Syndrome (GBS) is the most common cause of acute neuromuscular paralysis in the world. It is characterized clinically by acute, progressive, and generally ascending muscle weakness, loss of deep tendon reflexes, and paralysis. A recent systematic review estimated baseline incidence rates to be 1.2 cases per 100,000 person-years; rates increased with increasing age and male gender.¹ The etiology of GBS is not completely understood. It is hypothesized to be autoimmune in nature because many cases are preceded by acute respiratory or gastrointestinal infections.² There has been significant debate about associations between influenza-like illness, influenza vaccination and risk of developing GBS.³

Since the 1976 swine influenza vaccine campaign, surveillance for GBS after influenza vaccination has been a focal point of flu vaccine safety monitoring. During that campaign, a seven-fold increase in the incidence rate of GBS was observed among recipients of the swine origin influenza A (H1N1) subtype A/NJ/76 vaccine.⁴ Subsequent studies evaluating a possible GBS association with seasonal flu vaccination have demonstrated little or no elevated risk of GBS after vaccination and no conclusive evidence with regard to causality.

Surveillance for GBS was heightened during the 2009-2010 pandemic influenza A/H1N1 vaccination campaign. Immunization against both seasonal and pandemic H1N1 influenza strains is mandatory for uniformed members of the U.S. military. Safety monitoring of this program, including the monitoring of adverse events after vaccination, has been coordinated through the Armed Forces Health Surveillance Center (AFHSC) and the Military Vaccine Agency (MILVAX).⁵

Population-level surveillance for adverse events after vaccination often relies on administrative data bases for initial identification of possible cases through the use of ICD-9-CM diagnosis codes. However, the positive predictive value (PPV) of unverified diagnosis codes can vary greatly. For example, in a study evaluating seizure

events after receipt of a pneumococcal vaccine, the PPV was 97 percent if the seizure-related ICD-9-CM diagnostic code was assigned in an emergency department visit, but only 64 percent if the code was assigned during a hospitalization.⁶ Recently, Jones et al. reported on the poor specificity of hospital discharge diagnoses of GBS in a state health department hospital discharge dataset and reported that the PPV of a GBS diagnostic code (ICD-9-CM: 357.0) in a hospital record was only 30 percent.⁷ GBS was one of several outcomes that MILVAX monitored as part of its pandemic influenza A/H1N1 vaccine safety assessment. This report summarizes the results of the MILVAX chart confirmation of possible GBS cases (identified by AFHSC) and based on these findings, estimates the sensitivity, specificity, and PPV of different surveillance case definitions of GBS.

METHODS

The study conducted by MILVAX included two cohorts in the study population. The H1N1 cohort included all individuals who served in an active component of the Army, Navy, Air Force or Marine Corps who were vaccinated against the pandemic influenza A/H1N1 strain during the 2009-2010 vaccination season (November 1, 2009-April 30, 2010). The historical cohort included all individuals who served in an active component of the Army, Navy, Air Forces, or Marine Corps who received a seasonal influenza vaccine during November 1, 2008-April 30, 2009. Individuals who did not receive a seasonal influenza vaccine in the previous season or the monovalent pandemic influenza A/H1N1 vaccine during the 2009-2010 vaccination season were excluded to avoid selection bias due to vaccine contraindication.

Relevant medical encounter records were obtained from data routinely maintained in the Defense Medical Surveillance System (DMSS). Any medical encounter which included an ICD-9-CM code of 357.0 in any diagnostic position was selected as

a possible GBS case. The medical records of possible cases were reviewed by MILVAX (using a standardized medical chart abstraction form based on the Brighton Collaboration case definition) to determine which of the possible cases were confirmed ("true") cases.⁸

The sensitivity, specificity, and PPV of three different case definitions were calculated (Table 1). "Disease" status was considered positive if the MILVAX chart review classified the GBS case as confirmed. "Test" status was considered positive if the case was identified as a potential case through DMSS. "Sensitivity" represents the percentage of true cases identified by the test. In this case, DMSS identification of a GBS diagnosis represents the test. Specificity represents the percentage of individuals without the disease whose test is negative. PPV represents the percentage of people with a positive test who truly have the disease; in this case, it represents the proportion of all those individuals identified through an administrative case definition applied to data in the DMSS who were confirmed to have GBS during the chart reviews.

RESULTS

Sixty-one service members were identified as possible GBS cases. After detailed reviews of the medical records of the possible cases by MILVAX, 25 (41%) of the possible cases were confirmed as true cases. Of the confirmed GBS cases, all had at least one hospitalization with a GBS diagnostic code.

A surveillance case definition of GBS which required a hospitalization with a GBS-specific diagnostic code in any diagnostic position correctly identified all MILVAX confirmed cases of GBS. The sensitivity of this surveillance case definition was 100 percent, while the specificity was 81 percent and the PPV was 78 percent (Table 1a).

Requiring inclusion of at least one outpatient encounter with a GBS-specific code in any diagnostic position in addition to a GBS-related hospitalization increased specificity slightly (88%) and also increased

TABLE 1. Sensitivity, specificity, and PPV by case definition for GBS

		Disease status			
		+	-		
Screening test	+	a	b	Sensitivity	$a/(a+c)$
	-	c	d	Specificity	$d/(b+d)$
				PPV	$a/(a+b)$

a. One inpatient encounter

		Chart review			
		+	-		
DMSS definition a	+	25	7	32	Sensitivity 100%
	-	0	29	29	Specificity 81%
		25	36	61	PPV 78%

b. One inpatient and one outpatient encounter

		Chart review			
		+	-		
DMSS definition b	+	25	4	29	Sensitivity 100%
	-	0	32	32	Specificity 88%
		25	36	61	PPV 86%

c. One inpatient and one outpatient encounter with GBS diagnosis in the primary position

		Chart review			
		+	-		
DMSS definition c	+	23	3	26	Sensitivity 92%
	-	2	33	35	Specificity 92%
		25	36	61	PPV 88%

PPV to 86 percent. The sensitivity (100%) remained unchanged (**Table 1b**).

When the case definition included both a GBS-related hospitalization and one outpatient encounter, both with GBS-specific diagnostic codes in the primary (first-listed) diagnostic position, sensitivity decreased to 92 percent, but sensitivity and PPV both increased, to 92 and 88 percent respectively (**Table 1c**).

EDITORIAL COMMENT

This report estimates the sensitivity, specificity, and positive predictive value of

three different surveillance case definitions for GBS. Each of the case definitions had relatively high sensitivity, specificity, and PPV; for example, the observed sensitivities of two of the case definitions were 100 percent, while the PPV of the three definitions ranged from 78-88 percent. A single hospitalization with a GBS-specific ICD-9-CM diagnostic code in any diagnostic position had a PPV of 78 percent which is notably greater than the PPV of a similar definition applied to a state hospital discharge database.⁷ The design of this study used cases identified in DMSS as the starting point for the pool of cases upon which chart confirmation was performed. It is possible,

although unlikely, that some “true” cases of GBS never received a diagnosis code of 357.0 in the electronic medical record. This means that the values of sensitivity reported in this study may be higher than the true sensitivity (i.e., the sensitivity if all true cases of disease were included). All three definitions appear to have sufficiently good sensitivity and specificity to provide reliable and accurate identification of “true” cases of GBS. In public health surveillance scenarios where the need for case ascertainment is urgent (e.g., safety assessment of the pandemic influenza A/H1N1 vaccine), or when time-consuming and costly reviews of medical records to confirm diagnoses are not feasible, this methodology can be used to provide fast and accurate ascertainment of cases.

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Mental Health Diagnoses During the Year Prior to Schizophrenia, U.S. Armed Forces, 2001-2010

Maj Amy Costello, MD

Identification of military members in the prodromal phase of schizophrenia may lead to earlier treatment and allow non-urgent transition away from military duties. This report documents the incidence of schizophrenia in the U.S. military and summarizes mental health diagnoses during the year prior to initial clinical diagnoses schizophrenia. During 2001-2010, 3,000 service members met the case definition of schizophrenia (incidence rate: 21 per 100,000 person-years). Rates declined with increasing age. Of those diagnosed with schizophrenia, 71% had at least one mental health-related medical encounter during the preceding 12 months; 51% received at least one antecedent diagnosis of paranoia. The findings may inform a model to predict the likelihood and timing of clinical manifestations of schizophrenia among U.S. military members.

Schizophrenia is a chronic, disabling disease of unknown etiology. The disease is significant to the military partly due to demographics – young adults are at highest risk to develop the illness – and partly due to its devastating nature. A service member who is developing schizophrenia may manifest prodromal symptoms, including agitation, insomnia, lack of motivation, and decreased interaction, for months or years before an acute psychotic episode leads to a diagnosis.¹ Family and friends may attribute these symptoms to any number of causes, from stress to combat to drug abuse, or just bad behavior – until the first psychotic break. A service member in the prodromal phase of schizophrenia may be disruptive to the unit and divert resources from leadership and colleagues. Early identification of this prodrome may not only lead to earlier treatment for the patient, but also allow non-urgent transition away from military duties.

Although many genetic and environmental associations with schizophrenia risk have been identified, no definitive causal factor has been isolated. The disease is thought to affect about one percent of the US population over the age of 18.² Symptom onset is insidious, often beginning in adolescence and progressing until symptoms

become severe enough to mandate medical attention, typically during a patient's late teens or early twenties. Estimates of the male to female rate ratio for schizophrenia incidence range from 1.0 to 1.4.^{3,4} In one study, schizophrenia patients (at the time of diagnosis) were 15 times more likely than their peers to be unmarried. The World Health Organization estimates that schizophrenia is the eighth leading cause of disability-adjusted life years (DALYs) and the seventh leading cause of years of life lived with disability in people aged 15-44.⁴

During the prodromal phase of the disease, increasingly bizarre thoughts, social isolation, and decreased function at school or work may eventually lead the patient or his/her family to seek medical care.^{5,6} However, prodromal symptoms of schizophrenia are similar to those of many other psychiatric disorders and thus difficult to identify as a clinical syndrome. Clinical models have been developed to identify which patients with symptoms consistent with schizophrenia prodrome will progress to a diagnosis of schizophrenia.^{6,7} Validated scales, such as the Structured Interview for Prodromal Syndromes, in combination with a family history of schizophrenia, had positive predictive values of 65-80 percent in some academic psychiatric centers.^{8,9}

Efforts to delineate the prodromal syndrome and to develop a diagnostic tool have been successful enough that the prodromal phase is now being considered for inclusion in the Diagnostic and Statistic Manual V as a distinct diagnostic entity, "attenuated psychosis syndrome," with anticipated publication in May 2013.¹⁰ Diagnostic criteria for this syndrome include hallucinations, delusions, or disordered thought processes with intact reality testing. The criteria specify that the symptoms must be increasing in frequency and severity, and must be distressing enough that those affected seek help for them.

The concept of an identifiable prodrome raises the prospect that secondary prevention of schizophrenia might one day be possible. Early interventions are emerging and patients who are treated earlier in the course of their first psychotic episode have been shown to have better response to treatment, both in terms of reduction of symptoms and improved function.¹¹⁻¹²

In light of the potential value of identifying patients in the prodromal phase of schizophrenia, this report documents the incidence of schizophrenia diagnoses among military members and summarizes mental health diagnoses during the year prior to initial clinical diagnoses of schizophrenia.

METHODS

The surveillance period was 1 January 2001 through 31 December 2010. The surveillance population included all individuals who served in the active component of the Army, Navy, Air Force, Marine Corps, or Coast Guard at any time during the surveillance period. Data were derived from diagnoses recorded during hospitalizations or ambulatory visits in U.S. military and civilian (reimbursed care) medical treatment facilities and maintained in the

TABLE 1. Incidence rates of schizophrenia and number/percentage of mental health diagnoses in the 12 months preceding an incident schizophrenia diagnosis, active component, U.S. Armed Forces, 2001-2010.

	No.	%	Rate per 100,000 p-yrs	Incidence rate ratio	No. with antecedent mental health dx	% with antecedent mental health dx
Total	3,000	100	21	-	2,135	71
Sex						
Males	2,578	86	21	Ref	1,808	70
Females	422	14	20	0.96	327	77
Age at diagnosis						
17-24	1,788	60	32	Ref	1,196	67
25-29	713	24	22	0.66	547	77
30-34	288	10	14	0.41	224	78
35+	211	7	6	0.18	168	80
Race/ethnicity						
Black, non-Hispanic	776	26	31	Ref	545	70
White, non-Hispanic	1,602	53	18	0.57	1,164	73
Hispanic	309	10	21	0.69	222	72
Asian-Pacific Islander	181	6	28	0.89	118	65
American Indian	52	2	22	0.70	35	67
Marital status						
Single	2,218	74	37	Ref	1,492	67
Married	709	24	9	0.25	538	76
Other	66	2	12	0.32	55	83
Education level						
Less than high school	27	1	28	Ref	15	56
High school	2,531	84	25	0.88	1,795	71
Some college	183	6	17	0.58	138	75
College	139	5	9	0.31	106	76
Graduate	36	1	4	0.15	28	78
Service branch						
Army	1,462	49	29	Ref	1,102	75
Navy	692	23	20	0.68	438	63
Air Force	411	14	12	0.41	316	77
Marine Corps	402	13	22	0.76	253	63
Coast Guard	33	1	8	0.29	26	79
Pay grade						
E1-E4	2,538	85	41	Ref	1,745	69
E5-E9	375	13	7	0.16	318	85
O1-O5	84	3	4	0.10	70	83

Defense Medical Surveillance System. A case of schizophrenia was defined as an active component service member with at least one hospitalization or four outpatient encounters that were documented with schizophrenia-specific diagnoses (ICD-9-CM: 295). Schizophrenia cases that remained in active service for more than two years after meeting the surveillance case definition were assumed to have been misdiagnosed and removed from analysis. For purposes of characterizing prodromal clinical manifestations of schizophrenia, all mental health diagnoses (ICD-9-CM:

290-316, excluding 295) recorded during inpatient and outpatient encounters within 12 months preceding first diagnoses of schizophrenia were identified. Individuals who were considered incident cases of schizophrenia in 2001 were excluded from analyses if they received any schizophrenia diagnoses during the year 2000.

RESULTS

From 2001 through 2010, 3,000 service members met the case definition of

schizophrenia; the overall incidence rate was 21 per 100,000 person-years (p-yrs) (**Table 1**).

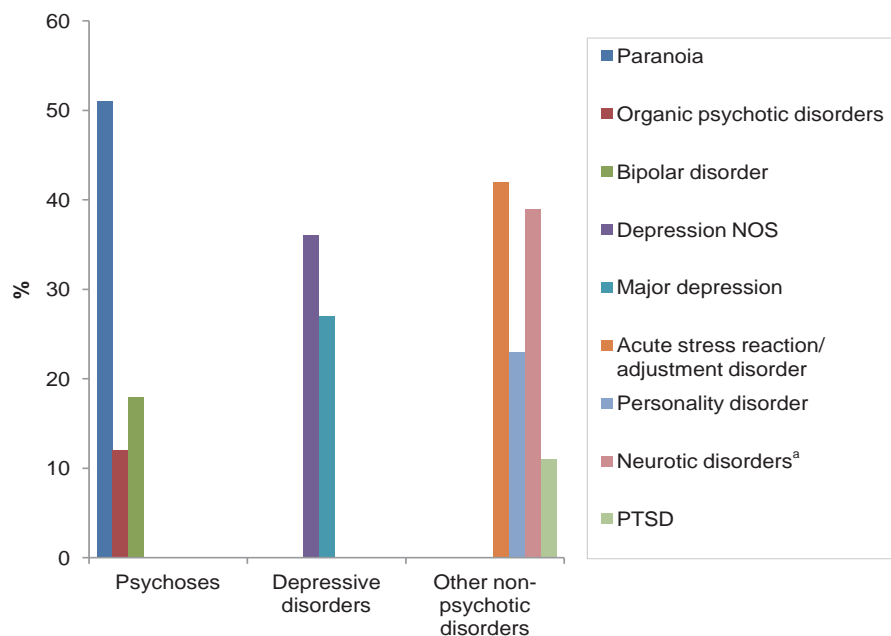
Incidence rates declined with increasing age, educational attainment, and military grade. For example, the incidence rate was more than four-fold higher among the youngest than oldest age group of service members (age group, incidence rate: 17-24 years, 32 per 100,000 p-yrs; >35 years, 6 per 100,000 p-yrs); approximately five times higher among junior than senior enlisted members; and approximately nine times higher among junior enlisted members than officers (**Table 1**).

Also of note, the crude incidence rate was more than three times higher among single (never married) than married service members; rates were higher among service members who were black, non-Hispanic and Asian-Pacific Islander than other racial/ethnic identities; and rates were similar among males and females (**Table 1**).

Time in service prior to diagnosis with schizophrenia ranged from 1 day to 26 years (**data not shown**). At the times of initial diagnoses with schizophrenia, approximately one of six (16%) cases were in their first 6 months, slightly more than one-half (56%) had between 6 months and 4 years, and the remainder (28%) had more than 4 years of active military service.

Of all active component members diagnosed with schizophrenia during the surveillance period, 71 percent had at least one mental health-related medical encounter during the 12 months preceding their first schizophrenia diagnosis (**Table 1**). Of all demographic and military subgroups of service members diagnosed with schizophrenia, senior enlisted members (85%), officers (83%) and those whose marital status was divorced, separated or widowed (83%) were the most likely to have documented antecedent mental health diagnoses; cases who had not completed high school (56%) were the least likely to have documented antecedent mental health diagnoses; and females and older cases were more likely than their respective counterparts to have documented antecedent mental health diagnoses. Among schizophrenia-diagnosed cases overall, airmen

FIGURE 1. Percentages of service members with common mental health diagnoses in the 12 months preceding an initial schizophrenia diagnosis (some patients may have been diagnosed with more than one condition), active component, U.S. Armed Forces, 2001-2010



^aNeurotic disorders included anxiety, hysteria, panic attacks, phobias, OCD, dysthymia, somatization and neurosis, NOS.

and Coast Guard members were the most likely, and sailors and Marines were the least likely, to have a mental health-related medical encounter within the year prior to their schizophrenia diagnoses.

Relatively frequent mental disorder-related diagnoses within the year prior to schizophrenia diagnoses included psychotic, depressive, and adjustment disorders (Figure 1). In the year prior to their schizophrenia diagnoses, the majority of cases (51%) received at least one diagnosis of paranoia and approximately 40 percent received diagnoses of neurotic disorders and acute stress reaction/adjustment disorders. Eleven percent were diagnosed at least once with PTSD.

EDITORIAL COMMENT

Schizophrenia is a disabling illness with enormous personal, societal, and financial costs. Patients with schizophrenia suffer from anosognosia (unawareness that they are ill) and paranoia. Such clinical expressions of schizophrenia make those affected unwilling to seek care; in turn, incidence rates are difficult to measure. However, U.S.

military members with frank psychosis are unlikely to escape detection and contact with the medical system. Service members experiencing prodromal symptoms who do not seek mental health care eventually will be referred to care by their supervisors. Once a diagnosis of schizophrenia is confirmed, the diagnosing physician must initiate a “Medical Evaluation Board” process to determine the patient’s fitness to continue military service. This, combined with access to “free” medical care and standardized electronic documentation of all medical encounters, results in a unique opportunity to document the incidence of schizophrenia in a young population.

This analysis found that incidence rates of schizophrenia among active component service members decreased with age; the finding is consistent with those of studies in other populations. Also, this report documented that incidence rates declined with increasing formal educational attainment and military grade; also, the incidence rate was three times higher among never married than currently or previously married service members. However, all of these characteristics are related to age; and in this analysis, there were not

adjustments to account for the effects of age differences. Also, rates were very similar among males and females; however, these unadjusted rates do not account for differences between male and female service members in age, educational attainment, service branch, or other potentially confounding factors.

Of all service members diagnosed with schizophrenia, 71 percent had at least one mental health diagnosis, and more than one-half had a documented diagnosis of a psychosis, within the preceding 12 months. The percentages of individuals with antecedent mental health diagnoses increased with age; they were highest in older, higher ranking, previously married service members and lowest among service members who did not complete high school. The finding should be interpreted cautiously; for example, service members who were diagnosed with schizophrenia soon after entering military service would have had less time to clinically manifest, seek care for, and be clinically diagnosed with a mental disorder antecedent to schizophrenia.

This study was designed to measure the incidence of schizophrenia in the active component of the U.S. military. Generalizability of the findings to the general population of the U.S. is limited. For example, the risk of developing schizophrenia begins in adolescence; U.S. military members are at least 17 years old when they enter service. In addition, all military members pass physical and cognitive military entrance examinations before beginning service; hence, military members who are diagnosed with schizophrenia may have higher pre-morbid functioning than their civilian counterparts. Also, unlike civilians, military members have universal access to mental health services.

There are other limitations to this analysis that should be considered when interpreting the results. For example, many service members with prodromal symptoms may leave service (possibly due to disciplinary problems or poor job performance) prior to manifesting or being diagnosed with schizophrenia. Such individuals would not be identified as cases. Also, this analysis relied on ICD-9-CM diagnostic codes documented in administrative medical records. ICD-9-CM codes documented

in administrative records have been shown to reliably identify schizophrenia cases; still, it is worth noting that the diagnoses used to identify cases for this report were not confirmed by medical record reviews.¹³ Finally, patients may have obtained mental health care using a spouse's insurance or Military One Source – a telephonic and electronic referral system which links patients to and pays for civilian mental health care. Such encounters would not have been captured in this analysis. These concerns are mitigated by the finding of higher rates of prodromal encounters in married service members, and by the fact that Military One Source policy requires service members with serious mental health problems to be referred to the military health system for care.

This summary of the incidence of schizophrenia and its prodromal symptoms among U.S. military members provides direction for further areas of study. For example, multivariate analyses would be useful to estimate the independent effects of various demographic and military characteristics on schizophrenia risk. Also, the data used for this analysis could be combined with relevant and potentially informative data not available in electronic medical records; such data include family histories and genetic risk factors, clinical

descriptions of symptomatology, and measures of pre-morbid functioning (e.g., as defined by objective universal cognitive tests such as the Armed Services Vocational Battery ([ASVAB])). Such a comprehensive data set might be useful in developing a model to predict the likelihood and timing of clinical manifestations of schizophrenia among active component members of the U.S. military.

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Heat Injuries, Active Component, U.S. Armed Forces, 2011

In 2011, the number of service members treated for heat stroke ($n=362$) was higher than the number in 2010, but lower than the numbers in 2007-2009. Incidence rates of heat stroke were highest among males, service members in combat-specific occupations, in the Marine Corps and Army, and among those younger than 20 years of age. The number of service members treated for "other heat injury" was higher in 2011 ($n=2,652$) than in any of the four prior years; however, there were fewer hospitalizations for "other heat injuries" in 2011 than in recent prior years. In contrast to heat stroke, the incidence rate of "other heat injuries" was higher among females than males and the rate among enlisted members was more than twice that of officers.

Heat-related injuries are significant threats to the health and operational effectiveness of military members and their units.^{1,2} Operational lessons learned and findings of numerous research studies have resulted in doctrine, equipment, and preventive measures that can significantly reduce the adverse health effects of military activities in heat.¹⁻³ Although numerous and effective countermeasures are available, physical exertion in hot environments still causes many hundreds of injuries - some life threatening - among U.S. military members each year.^{4,5}

In the U.S. Military Health System, the most serious of heat-related injuries are considered notifiable medical events. Since 31 July 2009, a notifiable case of "heat stroke" (ICD-9-CM: 992.0) has been defined as a "severe heat stress injury, specifically including injury to the central nervous system, characterized by central nervous system dysfunction and often accompanied by heat injury to other organs and tissue."⁶ Notifiable cases of heat injuries other than heat stroke ("unspecified effects of heat" [ICD-9-CM: 992.9]) include "moderate to severe heat injuries associated with strenuous exercise and environmental heat stress" ... "that require medical intervention or result in lost duty time." All heat injuries that require medical intervention or result in lost duty are reportable. Cases of "heat exhaustion" (ICD-9-CM: 992.3-992.5) that

do not require medical intervention or result in lost duty time are not reportable.⁶

This report summarizes heat injury-related hospitalizations, ambulatory visits, and reportable medical events among members of the active component during 2011 and compares them to recent prior years. Episodes of heat stroke and "other heat injuries" are summarized separately; for this analysis, "other heat injuries" includes "heat exhaustion" (which was reportable prior to 31 July 2009) and "unspecified effects of heat" (reportable since 31 July 2009).

METHODS

The surveillance period was 1 January 2007 through 31 December 2011. The surveillance population included all individuals who served in the active component of the Army, Navy, Air Force, Marine Corps, or Coast Guard at any time during the surveillance period. The Defense Medical Surveillance System (DMSS) was searched to identify all records of medical encounters and notifiable medical event reports that included primary (first-listed) or secondary (second-listed) diagnoses of "heat stroke" (ICD-9-CM:992.0) or "other heat injury" ("heat exhaustion" [ICD-9-CM:992.3-992.5] and "unspecified effects of heat" [ICD-9-CM:992.9]).

This report estimates numbers of individuals affected by heat injuries ("incident cases") and "heat injury events" during each calendar year. To estimate numbers of incident cases per year, each individual who was affected by a heat injury event (one or more) during a year accounted for one incident case during the respective year. To classify the severity of incident cases per year, those that were associated with any "heat stroke" diagnosis were classified as "heat stroke" cases; all others were classified as "other heat injury" cases.

To estimate numbers of heat injury events per year, affected individuals could account for multiple events during years. To discriminate follow-up encounters from new heat injury events, affected service members were not considered at risk of a "new" heat injury event within 60 days of a prior event. Annual numbers of heat stroke and "other heat injury"-related events were estimated separately. To categorize the clinical management of heat injury events, those that were documented with hospitalization records were classified as hospitalization cases; among the others, those documented with reportable event records were prioritized over those documented by ambulatory records only.

RESULTS

In 2011, there were 362 incident cases of heat stroke and 2,652 incident cases of "other heat injury" among active component members. Overall crude incidence rates of heat stroke and "other heat injury" were 0.25 and 1.82 per 1,000 person-years (p-yrs), respectively (**Table 1**).

In 2011, the incidence rate (unadjusted) of heat stroke was higher than the rate in 2010, but lower than the rates in 2007-2009; there were fewer heat stroke-related ambulatory visits in 2011 than any other year in the period, but more reportable events and hospitalizations than in 2010 (**Figure 1**).

TABLE 1. Incident cases^a and incidence rates^b of heat injury, active component, U.S. Armed Forces, 2011

	Heat stroke		"Other heat injury"	
	No.	Rate ^b	No.	Rate ^b
Total	362	0.25	2,652	1.82
Sex				
Male	341	0.27	2,099	1.68
Female	21	0.10	553	2.63
Age group				
< 20	51	0.62	568	6.90
20-24	148	0.31	1,108	2.35
25-29	88	0.24	520	1.44
30-34	43	0.19	229	1.03
35-39	22	0.13	141	0.85
40+	10	0.07	86	0.56
Race/ethnicity				
White, non-Hispanic	236	0.25	1,681	1.78
Black, non-Hispanic	60	0.26	516	2.20
Other	66	0.24	455	1.64
Service				
Army	230	0.41	1,643	2.92
Navy	15	0.05	178	0.55
Air Force	10	0.03	317	0.96
Marine Corps	104	0.52	502	2.50
Coast Guard	3	0.07	12	0.29
Military status				
Enlisted	300	0.25	2,427	2.00
Officer	62	0.25	225	0.92
Military occupation				
Combat	145	0.50	624	2.15
Health care	40	0.33	164	1.37
Other	177	0.17	1,864	1.78

^aOne per person per year

^bRate per 1,000 p-yrs

The overall incidence rates (unadjusted) of "other heat injury" were the same in 2010 and 2011 (1.82 per 1,000 p-yrs) but both were higher than in 2007-2009; of particular note, the rate was over 50 percent higher in 2010 and 2011 than 2008. The combined totals of ambulatory visits and notifiable medical event reports for "other heat injury" were higher in 2010 and 2011 than in any prior year; however, there were fewer hospitalizations for "other heat injuries" in 2010 and 2011 than in 2009 (Figure 2).

In 2011, subgroup-specific incidence rates of heat stroke were highest among males (0.27 per 1,000 p-yrs), service members in combat-specific occupations (0.50 per 1,000 p-yrs), in the Marine Corps (0.52 per 1,000 p-yrs) and Army (0.41 per 1,000 p-yrs), and among those younger than 20 years of age (0.62 per 1,000 p-yrs). Heat stroke rates in the Marine Corps and Army were more than five-fold those of the

other services, and nearly two times higher among males compared to females. Of note, rates of heat stroke were similar among officers and enlisted members and across race/ethnicity-defined subgroups (Table 1).

In 2011, subgroup-specific incidence rates of "other heat injuries" were highest among service members younger than 20 years of age (6.90 per 1,000 p-yrs), in the Army and Marine Corps (2.92 and 2.50 per 1,000 p-yrs, respectively), and in combat-specific occupations (2.15 per 1,000 p-yrs). In contrast to heat stroke experience, the crude incidence rate of "other heat injuries" was higher among females than males and the rate among enlisted members was more than twice that of officers (Table 1).

In 2011, 442 heat stroke events affected 362 individuals (average number of heat stroke events per affected individual: 1.22); 68 individuals experienced more than one heat stroke event during the year. The number of service members affected by more

than one heat stroke event in 2011 was lower than the average per year (n=97) during the prior years of the period. Also, in 2011, 2,904 "other heat injury" events affected 2,861 individuals (average number of other heat injury events per affected individual: 1.02); 42 individuals experienced more than one "other heat injury" event during the year. The number of service members affected by more than one "other heat injury" event in 2011 was lower than the average per year (n=76) during the prior years of the period (data not shown).

During the five-year surveillance period, heat-related injuries were diagnosed at more than 200 military installations/geographic locations worldwide. However, three Army installations accounted for more than one-third of all heat injury events during the period (Fort Bragg, NC [n=2,363], Fort Benning, GA [n=1,560], Fort Jackson, SC [n=920]); and four other installations accounted for an additional one-fifth of heat injury events (Parris Island/Beaufort, SC [n=899], MCB Camp Lejeune/Cherry Point, NC [n=659], Fort Polk, LA [n=555], Fort Campbell, KY [n=508]). Of the ten installations with the most heat injury events, eight are in the southeastern United States (Table 2).

FIGURE 1. Incident cases and incidence rates of "heat stroke," by source of report and year of diagnosis, active component, 2007-2011

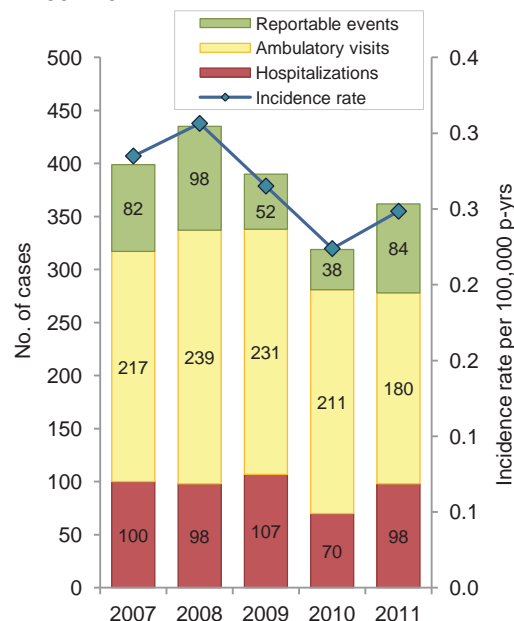
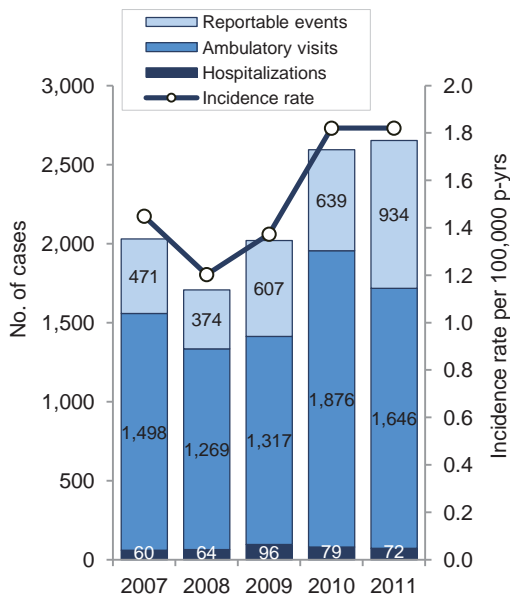


FIGURE 2. Incident cases and incidence rates of “other heat injury,” by source of report and year of diagnosis, active component, 2007-2011



EDITORIAL COMMENT

From 2008 through 2010, rates of heat stroke among U.S. service members declined, but the rate increased slightly in 2011. Rates of other clinically significant heat-related injuries increased during 2008 through 2010 and stabilized in 2011. In 2011, there were more hospitalizations for heat stroke than 2010 and more reportable events for “other heat injuries” than in recent prior years.

The results of this update should be interpreted with consideration of its limitations. For example, clinical criteria for mandatory reporting of heat-related injuries as “heat stroke” or “other heat injury” cases changed in 2009. Since that time, central nervous system dysfunction had to be present for a heat casualty to qualify as a case of “heat stroke.” Prior to the 2009 change, cases of “heat stroke” need not have exhibited nervous system dysfunction and the diagnosis could have been applied to patients with just laboratory evidence of injury to the liver, muscles, or kidneys. The change likely affected the numbers and natures of heat injury-related notifiable medical event reports in 2009-2011. In addition, similar heat-related

clinical illnesses are likely managed differently and reported with different diagnostic codes at different locations and in different clinical settings. Such differences undermine the validity of direct comparisons of rates of nominal “heat stroke” and “other heat injury” events across locations and settings. Also, this update is based on records of medical encounters at fixed (e.g., not deployed or at sea) medical facilities. As a result, heat injuries during training exercises and deployments that are treated in field/deployed medical facilities are not ascertained as cases for this report.

In spite of its limitations, this report documents that heat injuries are still a significant threat to the health of U.S. military members and the effectiveness of military operations. Of all military members, the youngest and most inexperienced Marines and soldiers (particularly those training at installations in the southeastern United States) are at highest risk of heat injuries - including heat stroke, exertional hyponatremia, and exertional rhabdomyolysis (see the other articles in this issue of the *MSMR*).

Commanders, small unit leaders, training cadre, and supporting medical personnel, particularly at recruit training

centers and installations with large combat troop populations, must ensure that military members whom they supervise and support are informed regarding risks, preventive countermeasures (e.g., water consumption), early signs and symptoms, and first responder actions related to heat injuries.¹⁻³ Leaders should be aware of the dangers of insufficient hydration on the one hand and excessive water intake on the other; they must have detailed knowledge of, and rigidly enforce countermeasures against, all types of heat injuries.

Policies, guidance, and other information related to heat injury prevention and treatment among U.S. military members are available on-line at: <http://chppm-www.apgea.army.mil/heat/#PM> and <http://www.marines.mil/news/publications/Documents/MCO%206200.1E%20W%20CH%201.pdf>.

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TABLE 2. Heat injury events^a by location of diagnosis/report, active component, U.S. Armed Forces, 2007-2011

Location of diagnosis	No.	%
Fort Bragg, NC	2,363	16.2
Fort Benning, GA	1,560	13.4
Fort Jackson, SC	920	7.9
Parris Island/Beaufort, SC	899	7.7
MCB Camp Lejuene/Cherry Hill, NC	659	5.7
Fort Polk, LA	555	4.8
Fort Cambell, KY	508	4.4
Camp Pendleton, CA	336	2.9
Fort Hood, TX	330	2.8
Fort Stewart, GA	300	2.6
MCB Quantico, VA	290	2.5
Fort Sill, OK	289	2.5
NMC San Diego, CA	231	2.0
Okinawa, Japan	229	2.0
All other locations	5,108	35.0
Total	14,577	100.0

^aOne heat injury per person per 60 days

Update: Exertional Rhabdomyolysis, Active Component, U.S. Armed Forces, 2011

In 2011, there were 435 incident episodes of rhabdomyolysis likely due to physical exertion and/or heat stress (“exertional rhabdomyolysis”) among U.S. service members. The annual rates of exertional rhabdomyolysis nearly doubled from 2007 to 2011. The highest incidence rates occurred in males, black, non-Hispanics, service members younger than 20 years of age and in the Marine Corps and Army. Most cases were diagnosed at installations that support basic combat/recruit training centers or major Army and Marine Corps combat units. Medical care providers should consider exertional rhabdomyolysis in the differential diagnosis when service members – particularly recruits – present with muscular pain, swelling, limited range of motion, or the excretion of dark urine possibly due to myoglobinuria after strenuous physical activity, particularly in hot, humid weather.

Rhabdomyolysis is the breakdown of striated muscle cells with release into the bloodstream of their potentially toxic contents. In U.S. military members, rhabdomyolysis is a significant threat during physical exertion, particularly under heat stress. Each year, the *MSMR* summarizes numbers, rates, trends, risk factors and locations of occurrences of exertional heat injuries, including exertional rhabdomyolysis. This update covers calendar year 2011. Information regarding the definition, causes and prevention of exertional rhabdomyolysis can be found in previous issues of the *MSMR*.¹

METHODS

The surveillance period was 1 January 2007 to 31 December 2011. The surveillance population included all individuals who served in an active component of the U.S. Armed Forces any time during the surveillance period. The Defense Medical Surveillance System was searched for records of health care encounters (inpatient or outpatient) associated with diagnoses related to the occurrence of exertional rhabdomyolysis. For surveillance purposes, a case of “exertional rhabdomyolysis” was defined as a hospitalization or ambulatory

visit with a discharge diagnosis in any position of: “rhabdomyolysis” (ICD-9-CM: 728.88) and/or “myoglobinuria” (ICD-9-CM: 791.3); plus a diagnosis in any position of “volume depletion (dehydration)” (ICD-9-CM: 276.5) and/or “effects of heat” (ICD-9-CM: 992.0-992.9) and/or “effects of thirst (deprivation of water),” “exhaustion due to exposure,” and “exhaustion due to excessive exertion (overexertion)” (ICD-9-CM: 994.3-994.5). Each individual could be included as a case only once per calendar year.

To exclude cases of rhabdomyolysis that were secondary to traumatic injuries, intoxications, or adverse drug reactions, medical encounters with diagnoses in any position of “injury, poisoning, toxic effects” (ICD-9-CM: 800-999, except “sprains and strains of joints and adjacent muscles” ICD-9-CM: 992.0-992.9, 994.3-994.5, and 840-848) were excluded from consideration as “exertional rhabdomyolysis” case defining encounters.

RESULTS

In 2011, there were 435 incident episodes of rhabdomyolysis likely due to physical exertion and/or heat stress (“exertional rhabdomyolysis”) (Table 1). The crude

incidence rate was 29.9 per 100,000 person-years (p-yrs).

In 2011, relative to their respective counterparts, the highest incidence rates of exertional rhabdomyolysis affected service members who were male (33.3 per 100,000 p-yrs), younger than 20 years of age (60.4 per 100,000 p-yrs), black, non-Hispanic (42.6 per 100,000 p-yrs), and in the Marine Corps (71.6 per 100,000 p-yrs) or Army (33.7 per 100,000 p-yrs). The lowest incidence rates affected service members in the Coast Guard (7.2 per 100,000 p-yrs) and those older than 40 years (8.7 per 100,000 p-yrs) (Table 1).

There were more incident diagnoses of exertional rhabdomyolysis in 2011 than in any previous year of the period (Figure 1). The annual rates of exertional rhabdomyolysis increased during the five-year period, nearly doubling from 2007 to 2011 (16.5 and 29.9 per 100,000 p-yrs, respectively). From 2008 to 2010, the annual number of

FIGURE 1. Incident diagnoses of exertional rhabdomyolysis by type of medical encounter, active component, U.S. Armed Forces, 2007-2011

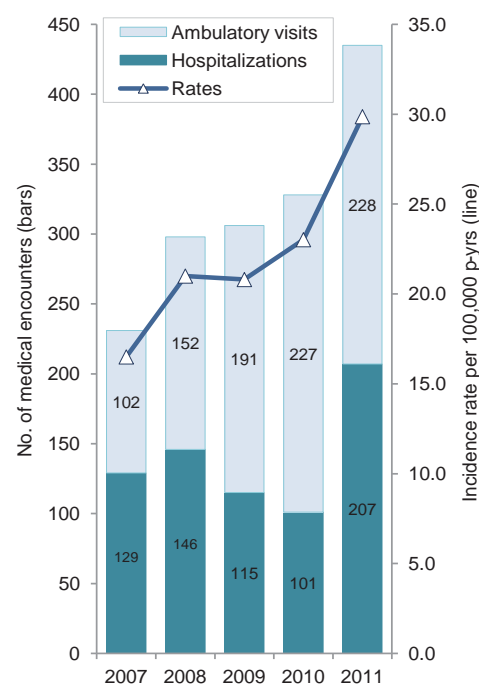


TABLE 1. Incident cases and incidence rates^a of exertional rhabdomyolysis, active component, U.S. Armed Forces, 2011

	Hospitalized		Ambulatory		Total	
	No.	Rate ^a	No.	Rate ^a	No.	Rate ^a
Total	207	14.5	228	15.7	435	29.9
Sex						
Male	200	16.4	215	17.3	415	33.3
Female	6	2.9	13	6.2	19	9.0
Age						
<20	25	24.2	39	36.8	64	60.4
20-24	77	16.1	98	20.3	175	36.2
25-29	55	16.3	45	12.8	100	28.5
30-34	29	14.0	23	10.6	52	24.0
35-39	14	8.6	18	11.1	32	19.7
40+	7	5.1	5	3.6	12	8.7
Service						
Army	93	17.1	97	17.2	190	33.7
Navy	18	5.7	22	6.8	40	12.5
Air Force	31	9.5	27	8.2	58	17.6
Marine Corps	64	32.4	80	39.8	144	71.6
Coast Guard	1	2.4	2	4.8	3	7.2
Race/ethnicity						
White, non-Hispanic	124	12.5	140	14.8	264	27.9
Black, non-Hispanic	45	19.1	55	23.4	100	42.6
Other	38	19.2	33	11.9	71	25.6
Rank						
Enlisted	175	14.8	199	16.4	374	30.9
Officer	32	13.2	28	11.4	60	24.4
Military occupation						
Combat	61	21.5	48	16.5	109	37.5
Health care	17	14.3	18	15.0	35	29.2
Other	129	12.6	162	15.5	291	27.8

^aRate per 100,000 p-yrs

hospitalized cases declined slightly while the number of cases diagnosed in outpatient settings increased; however, in 2011, the numbers of hospitalizations and outpatient visits were higher than in any of the previous four years (**Figure 1**).

In 2011, 76 percent of all service members hospitalized for exertional rhabdomyolysis were in the Army (n=93) and Marine Corps (n=64) (**Table 1**). Hospitalization rates increased in each service from 2010 to 2011 and remained highest in the Marine Corps (**Figure 2**). Among Marines, the rate of hospitalized cases declined in 2009 and 2010 to rates similar to the Army, but nearly tripled from 2010 to 2011. As in the past, in 2011 most cases occurred during the months of June to August (51% of the total) and May to September (72%) (**data not shown**).

During the five-year surveillance period, the medical treatment facilities at

five installations accounted for at least 49 cases each and more than 40 percent of all cases. Of these installations, two provide support to recruit/basic combat training centers (Marine Corps Recruit Depot [MCRD] Parris Island/Beaufort, SC; and Fort Jackson, SC;) and three support large combat troop populations (Fort Bragg, NC; Camp Pendleton, CA; and Camp Lejeune/Cherry Pt, NC) (**Table 2**). The most cases overall (accounting for 29% of all cases) were reported from Fort Bragg, NC (n=254) and MCRD Parris Island/Beaufort, SC (n=202) (**Table 2**).

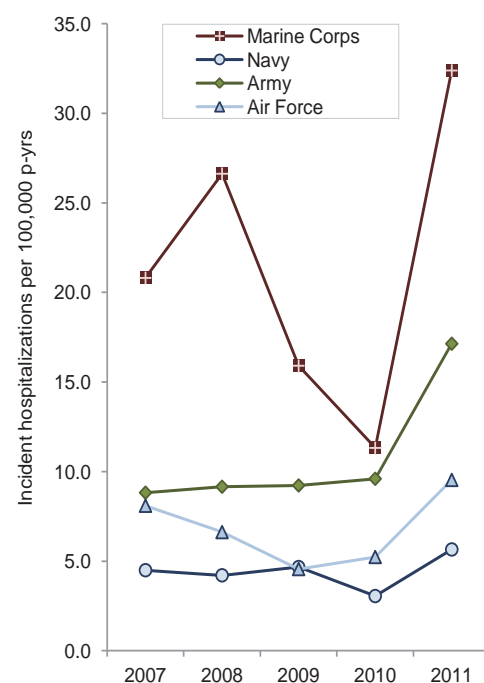
EDITORIAL COMMENT

This report documents a continuing increase in incident diagnoses of presumably exertional rhabdomyolysis among active component members of the U.S.

military. Most cases were diagnosed at installations that support basic combat/recruit training centers or major Army and Marine Corps combat units. The risks of heat injuries, including exertional rhabdomyolysis, are increased among individuals who suddenly increase overall levels of physical activity, recruits who are not physically fit when they begin training, and recruits from relatively cool and dry climates who may not be acclimated to the high heat and humidity at training camps in the summer.^{2,3} Soldiers and Marines in combat units often conduct rigorous unit physical training, personal fitness training, and field training exercises regardless of weather conditions. It is not surprising, therefore, that recruit camps and installations with large combat units account for most exertional rhabdomyolysis cases.

The findings of this report should be interpreted with consideration of its limitations. A diagnosis of “rhabdomyolysis” alone does not indicate the cause. Ascertainment of probable cases of exertional rhabdomyolysis was attempted by using

FIGURE 2. Incidence rates of hospitalization for exertional rhabdomyolysis, by service active component, U.S. Armed Forces, 2007-2011



^aCoast Guard not shown due to small annual case counts

TABLE 2. Incident cases of exertional rhabdomyolysis (among installations with at least 25 cases during the period), active component, U.S. Armed Forces, 2007-2011

Location of diagnosis	No.	%
Fort Bragg, NC	254	15.9
MCRD Parris Is/Beaufort, SC	202	12.6
Camp Pendleton, CA	77	4.8
Fort Jackson, SC	58	3.6
Camp Lejeune/Cherry Pt, NC	49	3.1
Fort Benning, GA	45	2.8
San Diego, CA	38	2.4
Lackland AFB, TX	38	2.4
Fort Hood, TX	32	2.0
Portsmouth, VA	29	1.8
Washington, DC	28	1.8
Fort Stewart, GA	28	1.8
Fort Campbell, KY	28	1.8
Other locations	692	43.3
Total	1,598	100.0

a combination of ICD-9 diagnostic codes related to rhabdomyolysis with additional codes indicative of the effects of exertion, heat, or dehydration. Further, other ICD-9 codes were used to exclude cases of rhabdomyolysis that were secondary to trauma, intoxication, or adverse drug reactions.

The higher rate in black, non-Hispanic service members compared to other racial/ethnic subgroup members may reflect, at least in part, increased risk of exertional

rhabdomyolysis among individuals with sickle cell trait.⁴⁻⁶ Supervisors at all levels should assure that guidelines to prevent heat injuries are enforced for all service members. They should be vigilant for early signs of exertional heat injuries including rhabdomyolysis among all (particularly, black, non-Hispanic) service members.

The measures that are effective at preventing exertional heat injuries in general are indicated for preventing exertional rhabdomyolysis. In the military training setting, the intensity and duration of exercise and adherence to prescribed work-rest cycles during strenuous physical activities should be adapted not only to ambient weather conditions but also to the fitness levels of participants in strenuous activities. The physical activities of overweight and/or previously sedentary new recruits should increase gradually and be closely monitored. Water intake should comply with current guidelines and be closely supervised. Strenuous activities during relatively cool mornings following days of high heat stress should be particularly closely monitored; in the past, such situations have been associated with increased risk of exertional heat injuries (including rhabdomyolysis).⁷ Commanders and supervisors at all levels should be aware of and alert for early signs of exertional heat injuries and should aggressively intervene when dangerous conditions, activities, or suspicious illnesses are detected.

Finally, medical care providers should consider exertional rhabdomyolysis in the differential diagnosis when service members – particularly recruits – present with muscular pain, swelling, limited range of motion, or the excretion of dark urine possibly due to myoglobinuria after strenuous physical activity, particularly in hot, humid weather.

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From 1999 through 2011, there were 1,329 incident diagnoses of exertional hyponatremia among active component members. In 2011, there were more incident cases (n=183) than in any other year of the period and more than three-times as many cases as in 1999 (n=57). Crude incidence rates of exertional hyponatremia were highest among females, Marines, and those in the youngest and oldest age groups. The increased incidence in the U.S. military overall reflects sharply increasing rates in the Marine Corps and slight increases in the other services, particularly since 2005. Service members (particularly trainees and women) and their supervisors must be vigilant for early signs of heat-related illnesses and must be knowledgeable of the dangers of excessive water consumption and the prescribed limits for water intake during prolonged physical activity – e.g., field training exercises, personal fitness training, recreational activities – in hot, humid weather.

Hyponatremia, which is defined as a low concentration of sodium in the blood (i.e., serum sodium concentration <135 mEq/L), can have serious and sometimes fatal clinical effects.^{1,2} In otherwise healthy, physically active young adults (e.g., long distance runners, military recruits), hyponatremia is often associated with excessive water consumption, excessive sodium losses in sweat, and inadequate sodium intake during prolonged physical exertion (“exertional hyponatremia”), particularly during heat stress.¹⁻⁴

Acute hyponatremia creates an osmotic imbalance between fluids outside and inside of cells. The osmotic gradient causes water to flow from outside to inside the cells of various organs, including the lungs (“pulmonary edema”) and brain (“cerebral edema”). Swelling of the brain increases intracranial pressure which can decrease cerebral blood flow and disrupt brain function (e.g., hypotonic encephalopathy, seizures, coma). Without rapid and definitive treatment to relieve increasing intracranial pressure, the brain stem can herniate through the base of the skull, and life sustaining functions that are controlled by the cardio-respiratory centers of the brain stem can be compromised.¹⁻³

In the summer of 1997, Army training centers reported five hospitalizations of soldiers for hyponatremia secondary to

excessive water consumption during military training in hot weather – one case was fatal and several others required intensive medical care.⁵ In April 1998, the U.S. Army Research Institute of Environmental Medicine (USARIEM), Natick, Massachusetts, revised the guidelines for fluid replacement during military training in heat. The new guidelines were designed to protect service members not only from heat injury but also from hyponatremia due to excessive water consumption. The guidelines limited fluid intake regardless of heat category or work level to no more than 1½ quarts hourly and 12 quarts daily.⁶ There were fewer hospitalizations of soldiers for hyponatremia due to excessive water consumption during the year after compared to before implementation of the new guidelines.⁷

This report uses a surveillance case definition for “exertional hyponatremia” to estimate frequencies, rates, trends, geographic locations, and demographic and military characteristics of exertional hyponatremia cases among U.S. military members from 1999 through 2011.

METHODS

The surveillance period was 1 January 1999 to 31 December 2011. The

surveillance population included all individuals who served in an active component of the U.S. Armed Forces any time during the surveillance period.

For surveillance purposes, a case of exertional hyponatremia was defined as a hospitalization or ambulatory visit with a primary (first-listed) diagnosis of “hyposmolality and/or hyponatremia” (ICD-9-CM: 276.1) and no other illness or injury-specific diagnoses (ICD-9-CM: 001-999) in any diagnostic position; or both a diagnosis of “hyposmolality and/or hyponatremia” (ICD-9-CM: 276.1) and at least one of the following within the first three diagnostic positions (dx1-dx3): “fluid overload” (ICD-9-CM: 276.6), “alteration of consciousness” (ICD-9-CM: 780.0x), “convulsions” (ICD-9-CM: 780.39), “altered mental status” (ICD-9-CM: 780.97), “effects of heat/light” (ICD-9-CM: 992.0-992.9), or “rhabdomyolysis” (ICD-9-CM: 728.88).

Medical encounters were not considered case defining events if they included complicating diagnoses such as alcohol/illicit drug abuse; psychosis, depression, or other major mental disorders; endocrine (e.g., pituitary, adrenal) disorders; kidney diseases; intestinal infectious diseases; cancers; major traumatic injuries; or complications of medical care in any diagnostic position. Each individual could be included as a case only once per calendar year.

RESULTS

From 1999 through 2011, there were 1,329 incident diagnoses of exertional hyponatremia among active component members (Table 1). In 2011, there were 183 incident diagnoses of exertional hyponatremia (incidence rate: 12.6 per 100,000 person-years [p-yrs]) among active component members (Table 1).

During the 13-year period, the average number of incident cases per year was 102. In 2011, there were more incident cases than in any other year of the period and more than three-times as many cases as in

TABLE 1. Incident cases and incidence rates^a of exertional hyponatremia, active component, U.S. Armed Forces, 1999-2011

	2011		Total 1999-2011	
	No.	Rate ^a	No.	Rate ^a
Total	183	12.6	1,329	7.2
Service				
Army	72	12.8	482	7.3
Navy	26	8.1	182	4.0
Air Force	40	12.2	301	6.8
Marine Corps	42	20.9	343	14.4
Coast Guard	3	7.2	21	4.2
Sex				
Male	146	11.7	1,063	6.7
Female	37	17.6	266	10.0
Race/ethnicity				
White, non-Hispanic	129	13.7	925	7.4
Black, non-Hispanic	22	9.4	172	5.2
Other	32	11.5	232	8.9
Age				
<20	20	24.3	186	13.6
20-24	45	9.5	387	6.4
25-29	36	10.0	225	5.6
30-34	17	7.6	129	4.8
35-39	11	6.7	140	5.9
40+	54	35.4	262	13.6
Military occupation				
Combat	22	7.6	280	7.3
Health care	18	15.0	132	8.8
Other	143	13.7	917	7.0

^aRate per 100,000 p-yrs

the year with the fewest cases (1999, n=57). Of note, there were only slightly more cases in 2011 than 2010, and the rates during those years were nearly identical (**Table 1**, **Figure 1**).

In 2011 among the Services, the most cases were in the Army (n=72), but the highest overall incidence rate was in the Marine Corps (20.9 per 100,000 p-yrs) (**Table 1**). In the Marine Corps, the annual crude rate increased 3-fold during the surveillance period overall and by more than 2-fold between 2003 and 2010 (**Figure 2**). During the 13-year surveillance period overall, the crude incidence rate was highest in the Marine Corps (14.4 per 100,000 p-yrs), intermediate in the Army and Air Force (7.3 and 6.8 per 100,000 p-yrs, respectively), and lowest in the Coast Guard and Navy (4.2 and 4.0 per 100,000 p-yrs, respectively) (**Table 1**, **Figure 2**).

In 2011, 80 percent of exertional hyponatremia cases (n=146) affected males; however, the annual rate in 2011 among

females (17.6 per 100,000 p-yrs) was the highest annual rate among males or females during the entire surveillance period. During ten years of the surveillance period, the annual rate was higher among females than males; also, during the surveillance period overall, the rate was approximately 50 percent higher among females than males (**Table 1**).

In 2011, the annual incidence rate was higher among white, non-Hispanic than black, non-Hispanic or “other” racial/ethnic subgroup members; however, during the surveillance period overall, the rate was higher among service members with “other” racial-ethnic identities (e.g., Hispanic, Asian, Pacific Islander, Native American) compared to their white non-Hispanic and black non-Hispanic counterparts (**Table 1**). In 2011 and during the surveillance period overall, the highest age group-specific incidence rates affected the oldest (>39 years) and youngest (<20 years) service members. During the surveillance period, there were not consistent relationships between exertional hyponatremia rates and military occupational group (**Table 1**).

During the 13-year surveillance period, exertional hyponatremia cases were diagnosed at U.S. military medical facilities at more than 200 locations; however, six locations were affected by 30 or more cases each and accounted for one-third of all cases (**Table 2**). The location with the most cases overall was the Marine Corps Recruit

FIGURE 1. Incident diagnoses of exertional hyponatremia, active component, U.S. Armed Forces, 1999-2011

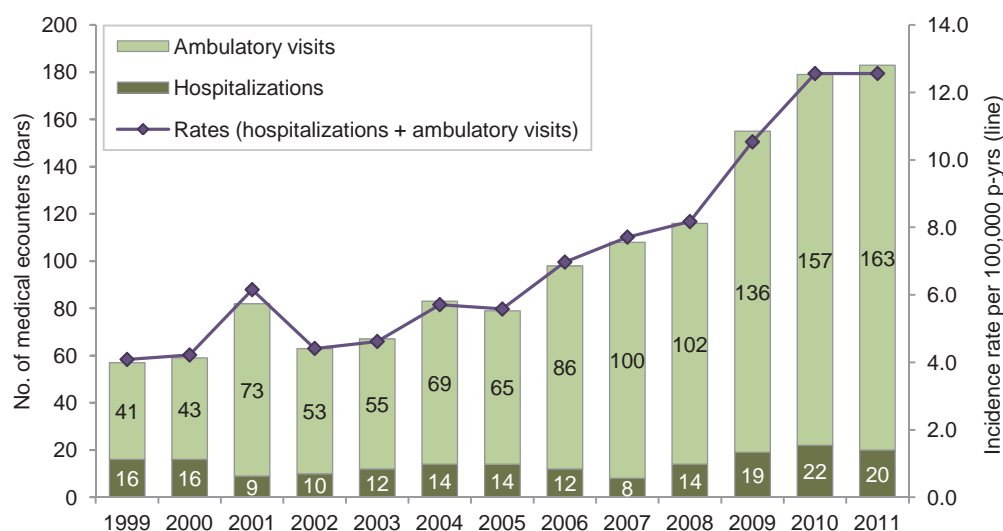
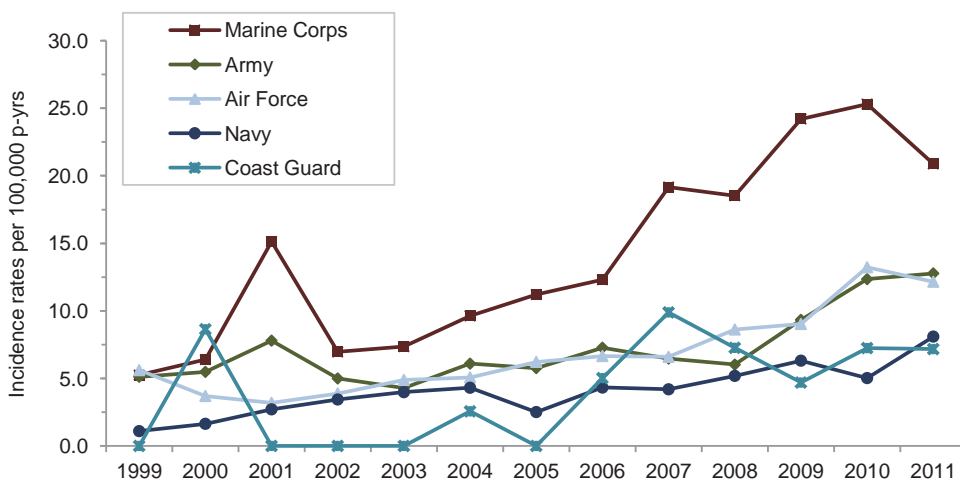


FIGURE 2. Incidence rates of exertional hyponatremia by service, active component, U.S. Armed Forces, 1999-2011



Depot (MCRD) Parris Island/Beaufort, SC (n=167); at MCRD Parris Island/Beaufort, there were 28 percent fewer cases in 2011 (n=23, 12.5% of the total) than 2009 (n=32, the peak of annual cases at any location overall) (data not shown).

considered estimates of the actual incidence of symptomatic exertional hyponatremia from excessive water consumption among U.S. military members. The accuracy of estimated numbers, rates, trends, and correlates of risk depends on the

completeness and accuracy of diagnoses that are reported on standardized records of relevant medical encounters. As a result, an increase in reporting of diagnoses indicative of exertional hyponatremia may reflect at least in part increasing awareness of, concern regarding, and aggressive management of incipient cases among military supervisors and primary health care providers.

In the past, concerns regarding hyponatremia from excessive water consumption were focused at training – particularly recruit training – installations. In this analysis, rates were relatively high among the youngest – hence, the most junior – service members, and the most cases were diagnosed at medical facilities that support large recruit training centers and large Army and Marine Corps combat units (e.g., MCRD Parris Island Beaufort, SC; Fort Benning, GA; Camp Lejeune/Cherry Point, NC; Fort Bragg, NC). In many circumstances (e.g., recruit training, Ranger School), military trainees rigorously adhere to standardized training schedules – regardless of weather conditions. In hot, humid weather, commanders, supervisors, instructors, and medical support staff must be aware of and enforce guidelines for work-rest cycles and water consumption.

In regard to hyponatremia, service members and their supervisors must be knowledgeable of the dangers of excessive water consumption and the prescribed limits for water intake during prolonged physical activity – e.g., field training exercises, personal fitness training, recreational activities – in hot, humid weather (**Figure 3**). Additional information can be found at: <http://www.usariem.army.mil/pages/download/tbmed507.pdf>

Women, who have higher rates of exertional hyponatremia in this report, may be at greater risk because of lower fluid requirements and longer periods of exposure to risk during some training exercises (e.g., land navigation courses, load-bearing marches).⁴ Service members (particularly trainees and women) and their supervisors must be vigilant for early signs of heat-related illnesses – and immediately and

EDITORIAL COMMENT

This report documents increases, in general, in the numbers and rates of exertional hyponatremia diagnoses among active component U.S. military members over the past 13 years. The increased incidence in the U.S. military overall reflects sharply increasing rates in the Marine Corps and slight increases in the other services, particularly since 2005.

The results of this report should be interpreted with consideration of several limitations. For example, there is not a diagnostic code specific for “exertional hyponatremia.” Thus, for surveillance purposes, cases of presumed exertional hyponatremia were ascertained from records of medical encounters that included diagnoses of “hyposmolality and/or hyponatremia,” but not other conditions that increase risk of hyponatremia in the absence of physical exertion or heat stress (e.g., metabolic, renal, psychiatric, iatrogenic). As such, the results of this analysis should be

TABLE 2. Incident cases of exertional hyponatremia by installation, active component, U.S. Armed Forces, 1999-2011

Location of diagnosis	No.	%
MCRD Parris Is/Beaufort, SC	167	14.6
Fort Benning, GA	79	6.9
MCB Camp Lejeune/Cherry Pt, NC	43	3.8
Fort Bragg, NC	35	3.1
MCB Camp Pendleton, CA	33	2.9
Fort Eustis, VA	32	2.8
NMC San Diego, CA	29	2.5
NMC Portsmouth, VA	28	2.4
Walter Reed AMC, DC	28	2.4
Fort Jackson, SC	27	2.4
MCB Quantico, VA	25	2.2
Lackland AFB, TX	24	2.1
NNMC Bethesda, MD	23	2.0
Fort Leonard Wood, MO	20	1.7
Fort Sam Houston, TX	20	1.7
Fort Shafter, HI	14	1.2
All other locations	519	45.3
Total	1,146	100.0

FIGURE 3. Fluid replacement guidelines for warm weather training (applies to average acclimated soldier wearing BDU, hot weather)

Heat category	WBGT Index, F	Easy work		Moderate work		Hard work	
		Work/rest	Water intake, qt/hr	Work/rest	Water intake, qt/hr	Work/rest	Water intake, qt/hr
1	78-81.9	NL	½	NL	¾	40/20 min	¾
2 (green)	82-84.9	NL	½	50/10 min	¾	30/30 min	1
3 (yellow)	85-87.9	NL	¾	40/20 min	¾	30/30 min	1
4 (red)	88-89.9	NL	¾	30/30 min	¾	20/40 min	1
5 (black)	>90	50/10 min	1	20/40 min	1	10/50 min	1

- The work/rest times and fluid replacement volumes will sustain performance and hydration for at least 4 hours of work in the specified heat category. Individual water needs will vary $\pm \frac{1}{4}$ qt/hr, and depending upon exposure to full sun or full shade, $\pm \frac{1}{4}$ qt/hr.
- NL= no limit to work time per hour.
- Rest means minimal physical activity (sitting or standing), accomplished in shade if possible.
- CAUTION: hourly fluid intake should not exceed 1½ quarts.
- Daily fluid intake should not exceed 12 quarts.
- Wearing body armor add 5 F to WBGT Index.
- Wearing MOPP over garment add 10 F to WBGT Index.

Easy work	Moderate work	Hard Work
Walking hard surface at 2.5 mph, <30lb load	Walking hard surface at 3.5 mph, <40lb load	Walking hard surface at 3.5 mph, \geq 40lb load
Weapon maintenance	Walking loose sand at 2.5 mph, no load	Walking loose sand at 2.5 mph, with load
Manual of arms	Calisthenics	Field assaults
Marksmanship training	Patrolling	
Drill and ceremony	Individual movement techniques, i.e., low crawl, high crawl	
	Defensive position construction	

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appropriately (but not excessively) intervene in such cases.

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